FATAL INTOXICATION WITH COLCHICINE

FERHAT ARIK[1], BADE ERTURK ARIK[2], OZERHAN OZER[1], UGUR KALAN[1], NUR UYANIKER[3], ALI CETINKAYA[1]
[1]Kayseri Training and Research Hospital, Department of Internal Medicine, Kayseri, Turkey - [2]Erciyes University, Faculty of Medicine, Department of Family Physicians, Kayseri, Turkey - [3]TSGI Engineering & Construction Company, Department of Quality, Aliağa, İzmir, Turkey

ABSTRACT

Introduction*: Colchicine is a medication with anti-inflammatory properties, which is used in gouty arthritis, familial Mediterranean fever (FMF) and consequently developing amyloidosis. Colchicine poisoning is associated with a bad outcome and can be fatal. Deaths generally occur because of hypovolemic shock and cardiovascular collapse or secondary to rapidly progressive multiorgan failure.*

Case presentation*: The present study is about a 20-year-old female patient who had taken 20 tablets of 0.5 mg/tb colchicine (0.2 mg/kg) for suicidal purpose. The treatments applied at each stage are explained with details.*

Conclusion*: Colchicine has a narrow therapeutic index and no clear-cut distinction between non-toxic, toxic, and lethal doses. In our case, the patient who had taken low-dose colchicine (0.2 mg/kg) died despite of all the treatments. Death with a such low dose is rare.*

Keywords*: Low dose, Colchicine, Intoxication, Fatal, Hemodialysis.*

DOI: 10.19193/0393-6384_2017_4_087

Received *November 30, 2016;* ***Accepted*** *March 20, 2017*

Introduction

Colchicine is a lipophilic alkaloid extract, which is isolated from Colchicum autumnale and Gloriosa superba. Colchicine has been using for centuries for the treatment of acute gout and has been approved by the Food and Drug Administration (FDA) for gout prophylaxis and treatment of FMF, which can reduce the incidence of the primary complication, systemic amyloidosis[1]. Colchicine may also play a role in the treatment of various other conditions such as recurrent pericarditis, scleroderma, Behcet's syndrome, and Sweet's syndrome but the data is often limited and inconclusive[2, 3].

Colchicine, which passes into systemic circulation following the oral ingestion, undergoes extensive first-pass metabolism in the liver and has low bioavailability of approximately 25 to 50%[4, 5]. Colchicine is substantially excreted by the liver after it is metabolized through deacetylation in the healthy individuals; approximately 20% is excreted by the kidneys[4, 6]. Colchicine metabolized in the liver is excreted via the bile into the intestinal tract. It is absorbed from the intestine again and undergoes enterohepatic re-circulation. Kidneys come to the foreground in patients with liver failure[7, 8]. Colchicine is highly distributed into the tissues and binds to microtubules, which are intracellular proteins after ingestion.

Colchicine inhibits the polymerization of the microtubules by binding to them, which have numerous functions such as communication, transport, movement, and transport of vesicle responsible for intracellular signal transmission, segregation of chromosomes during the metaphase stage of mitosis. Its anti-inflammatory effects occur due to these effects, it has an antimitotic effect at toxic doses[9]. The antimitotic effect is particularly evident in rapidly proliferating cells, for example, adverse events including nausea, vomiting, abdominal pain, diarrhea occur by affecting gastrointestinal cells, pancytopenia by affecting the bone marrow[10].

Colchicine has a narrow therapeutic index. At excessive doses, colchicine can cause serious systemic toxicity. Acute colchicine poisoning is uncommon, but few case reports encountered in the literature indicated that colchinine poisoning is associated with high mortality rate. Death usually occurs 36 to 72 hours after ingestion, as a result of hypovolemic shock, central nervous system toxicity or cardiopulmonary failure[11].

The purpose of this study is to discuss the clinical effects, treatments and outcomes of colchicine poisoning. There is no clear-cut distinction between non-toxic, toxic and lethal doses[12]. Even if it is rare, death is also reported with the ingestion of low dose (7-26 mg) as in our case

Case Presentation

A 20-year-old female patient with body weight of 50 kg ingested for suicidal purpose, 20 tablets of colchicine 0.5 mg/tb (0.2 mg/kg) which were used by her mother for FMF. The patient, who had nausea and vomiting after 1 hour of the ingestion of the drug and then had diarrhea, was admitted to emergency department after 8 hours. Information about possible complications and treatment was obtained from Poison Consultancy. The patient, who underwent gastric lavage in the emergency department, was administered active charcoal treatment. On the first examination, she was conscious, oriented, and cooperative; the patient who had diarrhea had also menstrual bleeding for 3 days. Her blood pressure was 100/70 mmHg, pulse 70/minute, respiratory rate 20/minute, and fever 37°C. Abdominal examination revealed tenderness to the palpation but no defense and rebound. According to the first blood test results at the emergency department, there were no liver and kidney dysfunction. The patient did not suffer from anemia.

But high troponin I and creatine kinase myocardial band isoenzyme (CK-MB) values showed that cardiac damage had begun (Table 1). The patient was transferred to the Internal Intensive Care Unit. The blood gas resulted a primary respiratory acidosis and normal anion gap with metabolic acidosis (Table 2). The echocardiography examination of the patient, who was consulted with the cardiologist considering the cardiotoxic effect of colchicine, showed that hypokinesia of the inferior ventricular wall was developed and the ejection fraction was 55%. 19 hours after high dose drug intake, patient had clinical deterioration: pulse of 119/minute, blood pressure of 116/74 mmHg, respiratory rate of 39/minute, fever of 36.0°C. Troponin level increased up to 19.04 ng/ml. The case was discussed again with the cardiologist. Administration of carvedilol 12.5 mg every 12 hours and ECG monitoring were recommended. ST elevations were detected during ECG monitoring. Bicarbonate replacement was done for the patient who developed metabolic acidosis with increased anion gap and whose pH decreased progressively.

In the 26th hour of the high dose drug intake, the patient underwent endotracheal intubation and respiratory support with invasive mechanical ventilation was started when the pulse obtained as 133/minute, blood pressure as 83/51 mmHg, respiratory rate as 43/minute, fever as 36.5°C. Intravenous 0.9% sodium chloride replacement, norepinephrine at 0.11 microgram/kg/min rate were initiated for hypotension. The patient underwent hemodialysis in the 40th hour of the drug ingestion due to anuria and metabolic acidosis deteriorated despite the bicarbonate replacement. Cardiac arrest developed in the 30th minutes of the dialysis in the patient whose troponin and CK-MB increased during the follow-ups. The patient responded to cardiopulmonary resuscitation. Cardiopulmonary arrest developed for the second time in the patient who underwent hemodialysis again upon the continuation of lactic acidosis and anuria. The patient who failed to respond to cardiopulmonary resuscitation after a 55-minute intervention, died in the 44th hour of the drug ingestion.

Discussion

Colchicine is a neutral and liposoluble alkaloid. The mean half-life for its elimination after oral ingestion is 9 to 16 hours, which may be prolonged with the toxic doses[9]. Colchicine poisoning is a rare

	WBC K/µL	PLT K/µL	BUN mg/dl	CREA mg/dl	ALT u/l	AST u/l	LDH u/l	CK u/l	Trop I ng/m	CK-MB u/l	PTT (sec)	INR
On admission	8,43	252	9	0,8	12	11	-	194	1,32	92	24	1,21
12 hours	14,43	288	12	0,9	25	170	1620	616	19,04	136	68,3	4,52
24 hours	21,9	281	27	2,4	147	454	4087	1392	92,09	282	88,2	4,96
36 hours	38,55	214	13	2,1	357	543	6200	1879	>98	239	82,2	5,1

Table 1: Complete blood count, biochemistry measurements, coagulation tests.
WBC: White Blood Cells, PLT: Platelet, BUN: Blood Urea Nitrogen, Crea: Creatinine, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, LDH: Lactate Dehydrogenase, CK: Creatine Kinase, Trop I: Troponin I, CK-MB: Creatine Kinase Myocardial Band, PTT: Partial Thromboplastin Time, INR: International Normalized Ratio

	pH	pCO_2	pO_2	HCO_3	BE
On admission	7.295	48.4	31.7	22.8	-2.7
12 hours	7.319	28.7	49.9	14.3	-10.6
24 hours	7.075	52.7	23	14.8	-13.5
36 hours	6.836	81.9	11.4	13.1	-18.6

Table 2: The blood gas monitoring.
pCO_2: Partial Pressure of Carbon Dioxide, pO_2: Partial Pressure of Oxygen, BE: Base Excess, HCO3: Bicarbonate

event characterized by multiorgan involvement and a poor prognosis[13].

Colchicine intoxication symptoms are divided into three phases. Phase 1 occurs within the first 24 hours. It is dominated by the gastrointestinal symptoms, e.g. nausea, vomiting, diarrhea, hypovolemia, abdominal pain. Phase 2 occurs from day 1 to day 7 after ingestion of the medication, most of the deaths occur in this stage. Findings related to multiorgan damages e.g. respiratory distress syndrome, cardiac arrhythmias, heart attack, cardiac arrest, cerebral edema, seizures, bone marrow depression, pancytopenia, disseminated intravascular coagulopathy (DIC), renal failure, metabolic acidosis, hypokalemia, hyponatremia, and sepsis are observed at this stage. Phase 3 occurs from the 7th to 21st day after the ingestion and comprises the recovery period. Alopecia and rebound leukocytosis can be observed in this phase. Deaths are principally associated with cardiac arrhythmia, cardiac arrest, myelosuppression, sepsis and hemodynamic collapse[12, 14, 15].

Early diagnosis and treatment are important in colchicine poisoning. The first thing to do after diagnosis is to decontaminate the patient from the drug. The activated charcoal for this purpose reduces colchicine absorption and enterohepatic circulation[15]. The main treatment is to provide aggressive supportive care to prevent organ dysfunctions[16]. Early fluid hydration should be given and electrolyte deficiencies must be corrected.

Cardiac arrhythmias, rhabdomyolysis, renal insufficiency, disseminated intravasculer coagulation (DIC), hypotension and shock should be treated. Invasive mechanical ventilation may be required in patients with acute respiratory distress syndrome (ARDS). When bone marrow suppression occurs, attention must be paid to neutropenia and granulocyte-colony stimulating factor (G-CSF) can be used for this purpose. Antibiotics may be needed for possible infections.

Although the basic principles of treatment are supportive care, there are different treatment approaches tried by clinicians. Extracorporeal life support (ECLS) can be tried if medical therapy is inadequate when cardiogenic shock develops. Jouffroy R et al. successfully treated the patient who was poisoned by colchicine using ECLS[5]. Despite the positive effects on prognosis, the use of colchicine Fab fragment antibodies has not been routinely used due to the prevalence, cost, and difficulty of dose adjustment[12, 17].

In our case the patient received 0.2 mg/kg of colchicine and the first indication of poisoning was gastrointestinal symptoms. Although deaths are mostly in the intake above 0.5 mg/kg dose, supportive treatment was initiated in response to the possibility of serious consequences such as multiple organ failure and cardiac arrhythmias resulting in death.

It was aimed to reduce the enterohepatic circulation and absorption of the drug by giving gastric lavage and active charcoal at the emergency department. High levels of cardiac biomarkers showed that myocardial cells are affected by colchicine. Progressive elevation of cardiac biomarkers and ST elevation in electrocardiography (ECG) showed increased myocyte damage. Cardiac dysfunction and hypotension caused tissue hypoperfusion. Despite positive inotropic agent and fluid resuscitation, hypotension and deterioration of tissue perfusion could not be corrected. Invasive mechanical ventilation was applied to the patient who devel-

oped ARDS. Fresh frozen plasma (FFP) and cryoprecipitate were given due to the development of DIC. The effect of hemodialysis is limited because colchicine is widespread in the body and binds to tissues at high rates. Hemodialysis was performed because the patient had metabolic acidosis that could not be corrected by medical treatment and impaired renal function.

Brncic N. et al applied basic supportive care, intravenous hydration, inotropic agent, bicarbonate and FFP treatments but the patient died on the 3rd day[18]. Erden A. et al reported that one of the two patients who underwent platelet infusion, FFP, intravenous fluid hydration, positive inotrop and hemodialysis treatment died and lived the other patient. The patient who died had received 1 mg/kg of colchicine and living patient received 0.2 mg/kg of colchicine. Dose relation with death was interpreted as the most important prognostic factor[19].

In the present case, the patient died from poisoning with a lower dose (0.2 mg/kg) of colchicine, despite the aggressive supportive treatment.

Conclusion

Acute colchicine intoxication is a serious and life threatening condition with a high mortality rate. It should not be forgotten that even though the dose taken of the deaths mentioned in the literature are mostly above 0.5 mg/kg, but deaths may also occur with much lower doses. All patients with symptoms of poisoning regardless of the dose should be closely monitored in terms of side effects that may develop. Aggressive supportive care should be administered to patients with the onset of side effects.

References

1) Zemer D, Pras M, Sohar E, Modan M, Cabili S, Gafni J. Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. N Engl J Med. 1986; 314(16): 1001-5.
2) Adler Y, Finkelstein Y, Guindo J, Rodriguez de la Serna A, Shoenfeld Y, Bayes-Genis A, et al. Colchicine treatment for recurrent pericarditis. A decade of experience. Circulation. 1998; 97(21): 2183-5.
3) Bhat A, Naguwa SM, Cheema GS, Gershwin ME. Colchicine revisited. Ann N Y Acad Sci. 2009; 1173: 766-73.
4) Achtert G, Scherrmann JM, Christen MO. Pharmacokinetics/bioavailability of colchicine in healthy male volunteers. Eur J Drug Metab Pharmacokinet. 1989; 14(4): 317-22.
5) Rochdi M, Sabouraud A, Girre C, Venet R, Scherrmann JM. Pharmacokinetics and absolute bioavailability of colchicine after i.v. and oral administration in healthy human volunteers and elderly subjects. Eur J Clin Pharmacol. 1994; 46(4): 351-4.
6) Putterman C, Ben-Chetrit E, Caraco Y, Levy M. Colchicine intoxication: clinical pharmacology, risk factors, features, and management. Semin Arthritis Rheum. 1991; 21(3): 143-55.
7) Gout. Br Med J. 1974;1(5905):446-8.
8) Wallace SL, Omokoku B, Ertel NH. Colchicine plasma levels. Implications as to pharmacology and mechanism of action. The American journal of medicine. 1970; 48(4): 443-8.
9) Ben-Chetrit E, Levy M. Colchicine: 1998 update. Semin Arthritis Rheum. 1998;28(1):48-59.
10) Hood RL. Colchicine poisoning. J Emerg Med. 1994; 12(2): 171-7.
11) Guven AG, Bahat E, Akman S, Artan R, Erol M. Late Diagnosis of Severe Colchicine Intoxication. Pediatrics. 2002; 109(5): 971-3.
12) Finkelstein Y, Aks SE, Hutson JR, Juurlink DN, Nguyen P, Dubnov-Raz G, et al. Colchicine poisoning: the dark side of an ancient drug. Clin Toxicol (Phila). 2010; 48(5): 407-14.
13) Atas B, Caksen H, Tuncer O, Kirimi E, Akgun C, Odabas D. Four children with colchicine poisoning. Hum Exp Toxicol. 2004; 23(7): 353-6.
14) Murray SS, Kramlinger KG, McMichan JC, Mohr DN. Acute toxicity after excessive ingestion of colchicine. Mayo Clin Proc. 1983; 58(8): 528-32.
15) Borron SW, Scherrmann JM, Baud FJ. Markedly altered colchicine kinetics in a fatal intoxication: examination of contributing factors. Hum Exp Toxicol. 1996; 15(11): 885-90.
16) Jouffroy R, Lamhaut L, Petre Soldan M, Vivien B, Philippe P, An K, et al. A new approach for early onset cardiogenic shock in acute colchicine overdose: place of early extracorporeal life support (ECLS)? Intensive Care Med. 2013; 39(6): 1163.
17) Rouan SK, Otterness IG, Cunningham AC, Holden HE, Rhodes CT. Reversal of colchicine-induced mitotic arrest in Chinese hamster cells with a colchicine-specific monoclonal antibody. The American Journal of Pathology. 1990; 137(4): 779-87.
18) Brncic N, Viskovic I, Peric R, Dirlic A, Vitezic D, Cuculic D. Accidental plant poisoning with Colchicum autumnale: report of two cases. Croatian medical journal. 2001; 42(6): 673-5.
19) Erden A, Karagoz H, Gumuscu HH, Karahan S, Basak M, Aykas F, et al. Colchicine intoxication: a report of two suicide cases. Ther Clin Risk Manag. 2013; 9: 505-9.

Corresponding author
FERHAT ARIK
Kayseri Training and Research Hospital, Department of Internal Medicine, Kocasinan
Kayseri, 38030
(Turkey)